REMARKS

Applicant has amended the claims to overcome the objections to the claims. It is respectfully submitted that these amendments are formal in nature and do not raise any issues of new matter. For example, the spelling out of the acronyms of the genes when they first appear in the claims simply recite the common names of these genes which have been well-known in the art. Entry of the claim amendments and favorable reconsideration are respectfully requested.

Claim Objections

It is respectfully submitted that the above claim amendments have overcome the objections to the claims.

Provisional Double Patenting Rejections

Applicant will file a necessary terminal disclaimer to overcome the double patenting rejection if and when the claims are indicated to be allowable.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully submits that the above claim amendment to Claim 67 has overcome its rejection under 35 U.S.C. § 112, ¶ 2.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Applicants gratefully acknowledge the indication by the Examiner that the instant application is enabled with regard to methods of treating cancers in non-human mammals. The Office Action, however, continues to reject all claims for alleged lack of enablement, making a distinction between treatment methods for humans and non-human mammals. Applicant respectfully traverses.

It is respectfully submitted that the Office Action used an improper legal standard in asserting the above claim rejections and in distinguishing, arbitrarily, between human and non-human treatment methods. Furthermore, the reasoning of the rejection in the Office Action is also scientifically unsound.

As an initial matter, the claim rejections are improper because there are granted U.S. patents with method claims and without any *in vivo*, to say nothing about human clinical, data see e.g. U.S. Pat. No. 6,025,340. In addition, the only full paragraph on page 9 of Office Action continues to argue that *in vitro* models sometimes are not adequate in predicting *in vivo* efficacy. These arguments are no longer pertinent because Dr. Davies declaration has established the *in vivo* efficacy of the claimed treatment methods.

The concerns in the Office Action appear to be directed at the field of gene therapy in general, rather than the current invention in particular. A suspicion that gene-directed enzyme-prodrug therapy, in general, was not ready for broad clinical application at the claimed priority date is not evidence of non-enablement, which requires a fact-based argument based specifically on the claimed methods.

In indiscriminately refusing to allow any human clinical treatment method using gene-therapy, the Office Action advanced some very unattainable legal arguments, and also ignored the science underlying the instantly claimed methods. There is simply no basis whatsoever in the law that would allow distinguishing a human treatment method from a non-human treatment method.

Scientifically, it has been widely accepted that an animal in vivo model generally correlates with human treatment methods.

Well-established case law indicates that enablement does not depend upon a therapeutic method being ready for clinical application. See e.g. *In re Brana*, 51 F.3d 1560, 1567, 34USPQ2d 1436, 1442 (Fed Cir 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes expectation of further research and development. The stage at which an invention in this field is useful is well before it is ready to be administered to humans.") Although this case discusses the utility standard under 35 U.S.C. § 101, its reasoning is equally applicable to analyses under 35 U.S.C. § 112, ¶ 1 See e.g. MPEP § 2164.02 (citing *Brana* in discussing correlation between *in vitro* and *in vivo* models). Similarly, the MPEP states:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans). Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how

> the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

MPEP § 2107.03(III) (underline original)

The Office Action states that the Declaration by Dr. Davies submitted 24 January 2004 is not persuasive, ignoring Professor Davies qualifications and his well-supported and reasoned statements that the approach described in the instant application would be highly likely to succeed in humans, and the models used are recognized as correlating with the condition (human cancer). Applicant respectfully submits that it is improper for the Office Action to not to give weight to such "a persuasively supported statement of one skilled in the art." *In re Lindell*, 385 F.2d 453, 155 USPQ 521, 524 (CCPA 1967). The MPEP counsels that in the absence of evidence to the contrary, the examiner should accept such a persuasive argument. MPEP § 2164.02. The Office Action did not demonstrate there was any evidence to the contrary.

The Office Action cites and discusses several references ostensibly in support the lack of enable rejections. These references, however, do not support the positions in the Office Action.

Verma and Somia is cited to show that gene delivery is unpredictable. However, at least two forms of gene therapy present far fewer delivery challenges. *Ex vivo* transfection and direct intra-tumoral injection. Directly relevant to the instantly claimed gene-directed enzyme-prodrug therapy

methods, especially delivered by adenoviral vectors, the reference itself states: "[A]denoviral vectors are extremely useful if expression of the transgene is required for short periods of time. One promising approach is to deliver large numbers of adenoviral vectors containing genes for enzymes that can activate cell killing... to cancer cells. In this case, the cellular immune response will augment tumour killing." Verman and Somia, at 241, col. 2. Again, this is precisely the approach demonstrated in the instant application.

The Office Action discussed Meng and el-Deiry, suggesting that the use of viral vectors relies on viral tropism for targeted delivery. The instant application, however, makes no such connection. Targeted delivery for the instant method is provided by the use of tissue- or tumour-specific promoters. Similarly, this reference itself, at page 5, column 2, paragraph 2, states that: "The most direct route is intratumoral, which practically assures delivery to the target tissue. Furthermore, the existence of a bystander effect obviates the need to deliver the agent into every cell, and local delivery minimizes toxicity to the normal tissues, where the agent is not present."

Russell was discussed to support the argument that direct intratumoral inoculation may be low in efficiency. Again, whilst not trivializing the technical challenges, Russell also states (in 1994, more than four years before the priority date of the instant application) the following (page 1169, last paragraph to page 1170, first paragraph): "There are good theoretical arguments for exploring the use of replicating gene-transfer vectors for human cancer therapy. Such vectors should be derived from weakly pathogenic human viruses with initially broad

tissue tropism. Coat protein engineering and promoter engineering might be used successfully to narrow the tropism of the vector, enhancing its ability to target tumour cells. Killing of uninfected 'bystander' tumour cells could be achieved through prodrug activation by a vector-encoded enzyme." Such approaches are within the scope of the instantly claimed methods and the use of a weakly pathogenic human viral vector (if not, in this case, a replicating one) is demonstrated by the applicant with both *in vitro* and *in vivo* examples.

The Office Action cites Marshall to argue that there are apparent risks of insertional mutagenesis stemming from the use of integrating lentiviral vectors. This, however, at best relates to the risk/benefit balance of the claimed method, not whether the instantly claimed method is enabled under 35 U.S.C. § 112, ¶ 1. Enablement in accordance with the requirements of 35 USC s112 does not require the high standard applied to regulatory approval. Even if risk/benefit anslysis is relevant, the invention is concerned with the treatment of otherwise terminal diseases, and in such a situation, considerable amount of risks would be considered acceptable. In any vent, the instant invention does *not* depend on the use of such vectors and was exemplified using adenoviral vectors.

Gura is discussed to show that there are shortcomings of xenograft animal models. Although it is understood by those of skill in the art that results of experiments in animal models are not 100% predictive of the responses of human disease, it is widely accepted that such experiments provide useful screening and are among the best methods currently available. It should be noted that Gura points out that xenograft tumor models may be relatively insensitive for a

number of reasons and so be inefficient (column 2, last line to column 3, line 8). It follows that *positive* results using such a model especially indicates efficacy.

Finally, there are now several gene-directed enzyme-prodrug therapy methods under clinical trials (Sausville, 2004, Genes in the service of therapeutic index: progress for virus-directed enzyme prodrug therapy. J. Clin. Oncol. 22: 1535-1537, 2004; Palmer et al. Virus directed enzyme prodrug therapy: intratumoral administration of a replication-deficient adenovirus encoding nitroreductase to patients with resectable liver cancer. J. Clin. Oncol. 22:1546-1552, 2004; and Searle et al., 2004, Clinical trials and further improvements of prodrug activation gene therapy with E. coli nitroreductase. Eur. Soc. Gene Therapy Meeting Abstract) (copy attached as Exhibits 1-3). These clinical trials should be presumed by PTO personnel that gene-directed enzyme-prodrug therapy "is reasonably predictive of having the asserted therapeutic utility" (see MPEP, 2107.03(III), *supra*) and, in combination with the *in vivo* data submitted by Declaration, strongly demonstrate that the degree of clinical experimentation for the instantly claimed human treatment methods are likely going to succeed and would not require undue efforts. In short, the claim rejections under 35 U.S.C. § 112, ¶ 1 are improper and should be withdrawn.

In summary, applicant respectfully submits that all claims are in condition for allowance and earnestly solicit an early indication from the Examiner to that effect. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be

appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #010331.49927US).

Respectfully submitted,

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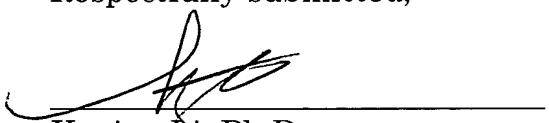

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